## REMARKS

Claims are pending in the instant application 1-36. Claim 1 has been amended and claim 37 has been added. Accordingly, claims 1-37 will be pending in the application upon entry of the instant amendment.

Support for the addition of claim 37 can be found throughout the specification and claims as originally filed. In particular, support can be found at least, for example, in claims 1 and 20 as originally filed and in the specification at page 5, lines 29-31 and page 10, lines 4-9. No new matter has been added.

Amendment of the claims herein should in no way be construed as acquiescence to any of the rejections/objections set forth in the instant Office Action, and was done solely to expedite prosecution of the above-identified application. Applicants reserve the option to prosecute the same or similar claims as those originally filed in the instant application or one or more or subsequent applications.

Attached hereto as Appendix A, captioned *"Version with markings to show changes made"*, is a marked-up version of the changes made to the claims by the amendments presented herein.

### *Claim Rejections-35 U.S.C. §112*

*Rejection of Claims 20-24 under 35 U.S.C. §112, Second Paragraph*

Claims 20-24 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants submit that the rejection no longer applies to claim 20 as amended herein, and claims 21-24 depending therefrom, or to new claim 37. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

***Claim Rejections - 35 U.S.C. §103***

*Rejection of Claims 1-36 under 35 U.S.C. §103(a)*

Claims 1-36 are rejected under 35 U.S.C. §103(a) as unpatentable over S. Scholl *et al.*, *J. Immunother.*, **23(5):** 570-580 (1997) in view of U.S. Patent 5,776,465 (1998) to O'Donnell *et al.* or U.S. Patent 5,591,632 O'Donnell *at al.* Applicants respectfully traverse the rejection.

In order to establish a *prima facie* showing of obviousness over the prior art, the Examiner must show the following three elements: (1) a suggestion or motivation to combine or modify the cited references; (2) a reasonable expectation of success; and (3) that the combination or modification of the prior art references teaches all the limitations of the claim at issue. Failure to show any one of the foregoing negates a *prima facie* showing. The initial burden is on the Examiner to provide some suggestion of the desirability of doing what the inventor has done. M.P.E.P. §2142 *et seq.*

Whether the rejection for obviousness depends on a combination of prior art references or a single reference alone, there must be some teaching, suggestion, or motivation to combine or modify the references. Usually, the suggestion comes from the teachings of the pertinent references, or from the ordinary knowledge of those skilled in the art that certain references are of special importance. It is clear that the suggestion or motivation cannot be derived from the teachings of the applicant. Therefore, when examining the patentability of a claimed invention that combines known elements, "the question is ***whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination***." *In re Rouffet*, 149 F.3d 1350, 1355-56 (Fed. Cir. 1998) (emphasis added); *see also*, *GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1462 (Fed. Cir. 1984); and *In re Beattie*, 974 F.2d 1309, 1311-12 (Fed. Cir. 1992). In other words, it not sufficient that the prior art ***could*** be so modified. Rather, the prior art must teach or suggest that the prior art ***should*** be modified. *See*, *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984).

Merely identifying all of the elements of a claim or their equivalents in the prior art is not sufficient. Almost all inventions are combinations of old elements, and an examiner may often find every element of a claimed invention in the prior art. If this finding were sufficient "to negate patentability, very few patents would ever issue." *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). Therefore, in order to establish a *prima facie* rejection for obviousness, an

"***examiner must show reasons*** that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would [*not* could] select the elements from the cited prior art references for combination in the manner claimed." *Id.*

The present invention generally provides a recombinant bacterium, *e.g. Mycobacterium bovis* bacillus Calmette-Guerin (BCG), engineered to secrete a cytokine, *e.g.*, IL-2, and to express a tumor antigen, *e.g.*, MUC1. Applicants have discovered that it is possible to engineer a bacterium that both secretes a cytokine and expresses a tumor antigen. Prior to Applicants' discovery, no one was able to achieve both secretion of a cytokine and expression of a tumor antigen by a single recombinant mycobacterium.

Scholl *et al.* describe the development of a recombinant vaccinia ***virus*** encoding human MUC1 cDNA and the gene for human IL-2, and preliminary immunotherapy trials of breast cancer using the recombinant virus. There is no teaching or suggestion in the reference of a recombinant ***bacterium*** that both secretes a cytokine and expresses a tumor antigen.

The two O'Donnell patents disclose recombinant BCG that express heterologous DNA encoding a tumor antigen ***or*** a cytokine. However, there is no teaching or suggestion in the patents of recombinant BCG bacterium that secretes a cytokine ***and*** expresses a tumor antigen.

The Examiner has taken the position that it would have been obvious for one of ordinary skill in the art at the time the invention was made to substitute the vaccinia virus of Scholl *et al.* with the multivalent BCG bacterium of the O'Donnell patents to arrive at the claimed invention. The Examiner asserts that the motivation to combine these references and make the substitution comes from the teaching in the O'Donnell patents that BCG vaccines have important advantages over presently available vaccines. Applicants respectfully disagree and traverse the rejection.

Applicants submit that there is no motivation in any of the cited references to combine the references in the manner suggested in the Official Action. First, one of ordinary skill in the art would recognize that viruses and bacteria are vastly different organisms with different morphology, biochemistry and properties. Indeed, these differences are art-recognized such that one of ordinary skill in the art would not consider the organisms to be equivalent biologically and therefore readily exchangeable. Moreover, Scholl et al. made a very positive report of their findings with the vaccinia virus vaccine, and few, if any, unsatisfactory finds were reported. ("The absence of serious adverse events together with the documentation of immune stimulation

*in vivo* warrant the further use of TG1031 in immunotherapy trials of breast cancer". Abstract, page 570, last sentence.) Further, there is nothing in the reference that suggests one should look for an alternative microorganism, much less a bacterium. Accordingly, what motivation would one of ordinary skill in the art have to look to the O'Donnell patents to look for another organism, especially a bacterium? The answer is that there is no motivation.

Second, the vaccinia virus vaccine of Scholl *et al.* would not be considered a "presently-available" vaccine as those terms are used in the context of the passage from the O'Donnell patents. The '632 patent issued from a patent application having a filing date of July 22, 1993. The '465 patent issued on a patent application having a filing date of June 5, 1995 which in turn was a continuation of the patent application from which the '632 patent issued. Both patent applications claim priority back to March 2, 1987. In contrast, the Scholl *et al.* reference was received for publication in September 1998 and published in 2000. Therefore, O'Donnell *et al.* would not have considered the vaccinia virus vaccine of Scholl et al. to be one of the "presently available advantages" over which their "subject invention as important advantages". Furthermore, one of ordinary skill in the art would not consider the vaccinia virus vaccine of Scholl et *al.* to be a vaccine that was available at the time the O'Donnell applications were filed and/or at the time the inventions disclosed and claimed therein were made.

Third, the biochemistry of the vaccinia virus of Scholl *et al.* and the mycobacterium (*e.g.*, BCG) is different and that difference has a significant effect on the immunologic response to the second protein (*e.g.*, MUC1) expressed by the recombinant mycobacterium. For example, in the case of the MUC1 protein, the protein is not glycosylated when expressed by the BCG mycobacterium. Aberrantly glycosylated (underglycosylated) MUC1 is specific to the malignant state of breast cancer. In contrast, the benign form of MUC1 is glycosylated. BCG is incapable of glycosylating MUC1.

However, a virus, such as vaccinia, will glycosylate MUC1. Thus, if a plasmid (vector) as recited in the instant claims is placed in a virus, the MUC1 protein expressed would be glycosylated, a chemical state indicative of the benign state, such that the glycosylated protein would not elicit an immunologic response that is specific for the tumor antigen.

In summary, there is no motivation in any of the cited references or any motivation that can be derived from the state of the art at the time the invention was made that would cause one

of ordinary skill in the art to combine the references in the manner suggested in the Office Action. Furthermore, because a virus would express a glycosylated the protein, resulting in a non-tumor specific immunologic response, one of ordinary skill in the art would not have a reasonable expectation of success in practicing the claimed invention. Accordingly, Applicants submit that the claimed invention is patentable over the cited references, taken alone or in combination, and respectfully request reconsideration and withdrawal of the rejection.

## CONCLUSION

In view of foregoing, entry of the amendments and remarks presented herein, favorable reconsideration and withdrawal of all rejections and objections, and allowance of this application with all the claims as amended herein are respectfully solicited.

If the Examiner believes that a telephone conversation with the Applicants' attorney would be helpful in expediting prosecution of this application, Examiner is invited to call the attorney of record at (617) 227-7400.

Respectfully submitted,

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Dated: July 28, 2003

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## APPENDIX A

***Version with Markings to Show Changes Made***

20. (Amended) An *E. coli*-BCG shuttle plasmid ~~which, when expressed in a mycobacterium, results in specificity for a tumor antigen and enhanced immunostimulatory properties, said shuttle plasmid~~ comprising:

(a) a first DNA molecule encoding a Th1 cytokine;

(b) a first promoter comprising DNA encoding a mycobacterial heat shock protein promoter and translational start site;

(c) a mycobacterial secretion signal sequence;

(d) a second DNA molecule encoding a tumor antigen; and

(e) a second promoter comprising DNA encoding mycobacterial heat shock protein promoter and translational start site;

wherein the 5' to 3' order is said first promoter of (b), said secretion signal sequence of (c), said first DNA molecule of (a), said second promoter of (e) and said second DNA molecule of (d), wherein the expression of said first DNA molecule of (a) is under the control of said first promoter of (b) and the cytokine is expressed and secreted from said mycobacterium in a biologically active form and the expression of said second DNA molecule of (d) is under the control of said second promoter of (e) ~~and the tumor antigen is expressed by said mycobacterium~~.